UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,582	02/13/2002	Francis E. Nano	2847-62205	9694

24197 7590 03/24/2004

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,582	NANO, FRANCIS E.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-33 are pending.

Applicant's preliminary amendment of claims 1, 8, 20, 22, 23, 25-33 and the specification, in a communication filed on 2/13/2002 are acknowledged.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/152,912 filed on 09/08/1999.

2. This application is the national stage of PCT/US00/24787 filed on 09/08/2000.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 2/13/2002 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 3, 8, 21, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 3 and 25 are indefinite in the recitation of "S-protein", "DsbA", "DsbC", "ketosteroid isomerase", "thioredoxin", "OmpT", "PelB" for the following reasons. These terms have been recited in

the claims as being detectable markers. However, as known in the art, these terms do not represent detectable markers. The Novagen Catalog 2001 teaches that the S-protein is a protein derived from pancreatic ribonuclease A that binds to proteins which comprise the S-tag. It is the S-tag, which is a 15 amino acid peptide, what can be used as a selectable marker (page 128). DsbA and DsbC are periplasmic enzymes which when fused to a recombinant protein, allow for enhanced solubility and proper folding (page 81). Therefore, they are not selectable markers. Ketosteroid isomerase (KSI) is used for the production of peptides since one can create a fusion comprising the KSI with the desired peptide for higher peptide yields. As such, KSI is not used as a detectable marker but as a "carrier" protein for production of peptides (page 77). Thioredoxin is used as a fusion protein with a target protein for enhancing the solubility of the target protein in a host cell, therefore it is not a selectable marker (page 78). OmpT is a protease and, as known in the art, strains deficient in this protease are used for the production of recombinant proteins, e.g. E. coli BL21, (page 68). PelB is a signal peptide which is normally used as a fusion protein with the target protein to facilitate secretion of the desired protein to the periplasmic space (page 72). As such, it is not known as a detectable marker. For examination purposes, no patentable weight will be given to these terms. Correction is required.

7. Claims 3 and 25 are indefinite in the recitation of "protein kinase A site" for the following reasons. This term has been defined as a selectable marker. As written, it appears that the detectable marker is a portion of the protein kinase A (PKA). However, as known in the art, as evidenced by The Novagen Catalog 2001, it is a 5 amino acid peptide which binds to the catalytic subunit of PKA what is used as a detectable marker (page 79). If this 5 amino acid peptide is the intended detectable marker, the claim should be amended to recite "protein kinase A recognition peptide" or similar. Correction is required.

8. Claim 8 is indefinite in the recitation of "wherein the one or more proteins expressed by the recombinant DNA molecule comprises a protein expressed from a promoter derived from a

psychrotrophic bacterial DNA" for the following reasons. First, proteins are not expressed by DNA molecules but rather by the host cell comprising the corresponding DNA molecule. In addition, the term "the one or more proteins ....comprises a protein expressed ..." is unclear since one cannot determine if the term "comprises" is equivalent to "is(are)". For examination purposes, it will be assumed that the term recites "wherein the recombinant DNA molecule is operably linked to a promoter derived from psychrotrophic bacteria". Correction is required.

9. Claim 21 is indefinite in the recitation of "a method of amplifying a nucleic acid molecule in a liquid wherein the liquid is treated by the method of claim 20" for the following reasons. The method of claim 20 is directed to the method of claim 15, which is directed to a method for enzymatically degrading a nucleic acid in a sample. As such, it is unclear as to how one can amplify any nucleic acid in a liquid which does not contain nucleic acids due to enzymatic degradation, as recited in claim 15. For examination purposes, it will be assumed that the claim recites "a method of amplifying a DNA molecule in a liquid wherein the liquid does not contain any RNA due to enzymatic degradation of said RNA by a heat labile nuclease". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 9-23 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9-20, 22-23, and 28-33 are directed to a method for removing/degrading proteins or nucleic acids by using a genus of heat-labile proteases/nucleases. Claim 21, as interpreted, is directed to a method for amplifying DNA in a liquid wherein the liquid contains no RNA due to enzymatic degradation by a genus of heat labile nucleases.

The written description requirement for a genus of compounds required to practice a claimed method may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus of compounds required to practice the claimed method. In the instant case, while the specification discloses (1) identification of protease activity in strain A9 and partial purification of a heat labile protease from strain A9, called protease A9 (pages 21-22), (2) identification of protease activity in strains C65, H6, C46, S20 (pages 23-24), and (3) identification DNAse activity in strains A9, F9, H6 and S20 (page 35), the specification fails to disclose the structure (i.e. sequence) of the A9 protease or DNase, other heat labile proteases/nucleases from psychrotrophic bacteria, relevant identifying characteristics associated with other heat labile proteases/nucleases from psychrotrophic bacteria, the structural characteristics which are common to all heat labile proteases/nucleases from psychrotrophic bacteria, as encompassed by the claims, the optimal temperature range at which all heat labile proteases/nucleases from psychrotrophic bacteria will be active, and the temperature range at which all heat labile proteases/nucleases from psychrotrophic bacteria will be inactivated.

The genera of heat labile proteases and nucleases required to practice the claimed method are extremely large and encompasses structurally and functionally diverse proteases/nucleases. Not a single structural feature has been disclosed which would be common to all members of the genus. The teachings

of the specification are insufficient to put one of ordinary skill in the art in possession of all attributes and features of the claimed method. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

12. Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for recombinantly producing proteins/transcription products by transforming the strains listed in Table 1 with recombinant DNA which is operably linked to the Tac promoter or a promoter derived from the strains listed in Table 1 of the specification, (2) a method for producing DNA molecules in the strains listed in Table 1 by introducing recombinant DNA molecules via plasmid pUI109 or plasmids derived from pRSF1010, (3) a method for degrading/removing proteins by using the protease A9, and (4) a method for identifying promoters that are active in the strains of Table 1 wherein said method uses plasmid pUI109 or plasmids derived from pRSF1010 to introduce a DNA construct comprising a polynucleotide encoding a selectable marker and a DNA fragment isolated from the strains in Table 1, does not reasonably provide enablement for (1) a method for producing proteins/transcription products by transforming any psychrotrophic bacteria with recombinant DNA which is operably linked to any promoter, (2) a method for producing DNA molecules in any psychrotrophic bacteria by introducing recombinant DNA molecules having any origin of replication, (3) a method for degrading/removing proteins by using any heat labile protease from psychrotrophic bacteria, (4) a method for degrading nucleic acids with any heat labile nuclease from psychrotrophic bacteria, or (5) a method for identifying a promoter that is active in any psychrotrophic bacteria using any vector/plasmid or DNA having any origin of replication. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 1-7 and 26-27 are directed to a method for producing proteins, DNA, or transcription products by (a) transforming any psychrotrophic bacteria with recombinant DNA for expression/production of proteins, DNA, or transcription products, and (b) exposing the bacteria to a temperature suitable for inactivating one or more enzymes in the bacteria. Claim 8 is directed to the method of claim 1 with the added limitation that the recombinant DNA is operably linked to a promoter derived from psychrotrophic bacteria. See claim interpretation above. Claims 9-20, 22-23, and 28-33 are directed to a method for removing/degrading proteins or nucleic acids by using any heat-labile proteases/nucleases from psychrotrophic bacteria. Claim 21, as interpreted, is directed to a method for amplifying DNA in a liquid wherein the liquid contains no RNA due to enzymatic degradation by any heat labile nuclease from psychrotrophic bacteria. Claims 24-25 is directed to a method for identifying a promoter active in any psychrotrophic bacteria by transforming said bacteria with a DNA molecule/vector comprising a DNA fragment and a polynucleotide encoding a detectable marker, wherein said DNA molecule/vector has any origin of replication.

The scope of the claims is not commensurate with the enablement provided by the specification in view of the extremely large number of unknown proteases and nucleases required to practice the claimed methods as well as the lack of information as to the temperature ranges for protein inactivation, promoters which would be operable in any psychrotrophic bacteria, and vectors or structural elements required for the DNA to be produced to replicate in any psychrotrophic bacteria.

In addition to the teachings of the specification described above, the specification discloses the use of the Tac promoter in strains C65, H6 and A9 for the expression of recombinant proteins (page 47) as well as introduction of recombinant DNA via conjugation using plasmids derived from pRSF1010 (broad host range plasmids; page 40) or plasmid pUI109 (page 39). The argument can be made that one can practice the claimed methods using the information disclosed in the specification and the prior art. However, the specification fails to disclose (a) other heat labile proteases or nucleases, (b) the structure of other proteases or nucleases, (c) identifying characteristics associated with other heat labile proteases/nucleases from psychrotrophic bacteria such that one of skill in the art can easily isolate and purify those proteases/nucleases, (d) the structural characteristics which are common to all heat labile proteases/nucleases from psychrotrophic bacteria, (e) temperature ranges at which all heat labile proteases/nucleases will be active or inactive such that one of skill in the art can determine the appropriate conditions to carry out the claimed method. Also, the specification does not disclose other promoters which can be used in any psychrotrophic bacteria such that expression can occur, or other plasmids/vectors which would allow replication of any DNA in any psychrotrophic bacteria. It is noted that not any bacterial promoter is expected to be functional in any psychrotrophic bacteria. Similarly, not any vector is expected to replicate in any psychrotrophic bacteria, as evidenced by the specification (pages 39-40) where the plasmids used were broad host range plasmids. As such, a method for producing DNA molecules in any psychrotrophic bacteria would require some knowledge as to the elements required in the DNA molecule to be produced that would allow replication in said bacteria. Furthermore, the art does not teach which are the structural characteristics which are common to all heat labile proteases/nucleases from psychrotrophic bacteria, the temperature ranges at which all heat labile proteases/nucleases are active or inactive, other promoters which can be used in any psychrotrophic bacteria, or other plasmids/vectors or structural elements which can be used in any psychrotrophic bacteria for DNA replication.

Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge in the art about structural/functional or other identifying characteristics for all the heat labile proteases/nucleases, promoters and vectors required to practice the claimed methods, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed methods. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

13. It is noted that if the claims are amended to recite limitations regarding the strains listed in Table 1, the enzymes derived from these strains, or specific plasmids, a biological deposit in accordance with 37 CFR 1.801-1.809 may be requested to comply with the enablement requirements.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 1-2 and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Gugi et al. (J. Bacteriol. 173(12):3814-3820, 1991; cited in the IDS).

Claim 1 is directed to a method for producing recombinant proteins by transforming a psychrotrophic bacterium, heat inactivating one or more enzymes of the bacterium, and isolating the

proteins. Claim 2 is directed to the method of claim 1 with the added limitation that the psychrotrophic bacterium is grown at no more than 30 C. Claims 26-27 are directed to the method of claim 1 wherein the inactivation of the bacterial enzymes is carried out at no more than 50 or 40 C, respectively.

Gugi et al. teaches the transformation of the psychrotrophic bacterium P. fluorescens with the E. coli appA gene encoding a phosphatase and expression of said phosphatase (page 3814, left column, second paragraph-page 3815, right column). Gugi et al. teaches the cultivation of the transformed P. fluorescens at 25 and 30 C (page 3815, left paragraph, line 6). Gugi et al. also teaches measurement of phosphatase activity by adding 0.5 M NaOH to the cells such that phosphatase would be released and could be measured (page 3815, left column, Enzymatic Assays). In addition, Gugi et al. teaches that cultivation at 30 C inactivates endogenous periplasmic P. fluorescens phosphatase activity (page 3817, left column, last 3 lines, right column, first 3 lines; Figure 4). Therefore, the teachings of Gugi et al. anticipate the claims as written.

15. Claims 9-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Ihns et al. (U.S. Patent No. 5861366, filed May 1996; cited in the IDS).

Claims 9, 11 and 13 are directed to a method for enzymatically degrading/removing a protein using a heat labile protease wherein the protease is inactivated at a temperature no higher than 60 C. Claim 10 is directed to the method of claim 9 with the added limitation that the protein degraded is a DNA ligase, DNA polymerase, RNA polymerase, endonucleases, RNases, DNases, alkaline phosphatases, exonucleases, DNA gyrases, reverse transcriptases, topoisomerases, and methylation enzymes. Claim 12 is directed to the method of claim 11 with the added limitation that the sample comprising the protein to be degraded also comprises other biological components selected from the group consisting of cells, organelles, carbohydrates, lipids, and nucleic acids.

Ihns et al. teaches a method of cleaning protein residues by using detergent compositions comprising proteases (column 11, lines 6-47). Ihns et al. also teaches that any protease residue remaining

on the item to be cleaned can be removed by inactivation at 60 C (column 11, lines 21-22). This reference also teaches that the products to be treated with the protease are foods such as milk, dairy products, beer, soups, yogurt, and puddings. As such, food products to be treated, such as yogurt, would contain cellular components such as carbohydrates, lipids, nucleic acids, as well as DNases, RNases, and other DNA/RNA related enzymes which would normally be found in cells. Ihns et al. discloses that one could use the protease to remove protein residues from food processing units. Therefore, the teachings of Ihns et al. anticipate the claims as written.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gugi et al. (J. Bacteriol. 173(12):3814-3820, 1991; cited in the IDS). The teachings of Gugi et al. have been discussed above. Since the transformed P. fluorescens cell of Gugi et al. expresses a recombinant protein, it also produces the recombinant DNA encoding the protein, and the mRNA encoding the protein (transcription

product). While the E. coli phosphatase produced can be detected, Gugi et al. does not teach the use of the detectable markers recited in claim 3, the isolation of the recombinant DNA encoding the E. coli phosphatase, or the isolation of the corresponding mRNA (transcription product).

Claim 3 is directed to the method of claim 1, as described above, wherein the recombinant protein expressed contains a detectable marker. Claims 4 and 6 are directed to a method for producing recombinant DNA or transcription products by transforming a psychrotrophic bacterium, heat inactivating one or more enzymes of the bacterium, and isolating the DNA or transcription products. Claims 5 and 7 are directed to the methods of claims 4 or 6 with the added limitation that the psychrotrophic bacterium is grown at no more than 30 C.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to transform a psychrotrophic bacterium, as taught by Gugi et al., with a recombinant DNA which comprises a polynucleotide which encodes a detectable marker and the desired protein. Also, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate the recombinant DNA or the transcription products produced by the P. fluorescens of Gugi et al. A person of ordinary skill in the art is motivated to transform a psychrotrophic bacterium, as taught by Gugi et al., with a recombinant DNA which comprises a polynucleotide encoding the desired protein and a detectable marker for the benefit of being able to detect and purify the recombinant protein. Also, a person of ordinary skill in the art is motivated to isolate the DNA or the mRNA made by the P. fluorescens cell of Gugi et al. for obtaining sufficient DNA/mRNA further characterization studies and/or additional transformation experiments. One of ordinary skill in the art has a reasonable expectation of success at producing the recombinant protein comprising the detectable tag since the use of detectable tags is well known and widely used in the art for purification purposes. Also, one of ordinary skill in the art has a reasonable expectation of success at isolating the DNA or the mRNA made by the P. fluorescens cell of Gugi et al. since DNA/RNA isolation is well known and widely practiced in the art. Therefore, the

invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

19. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Ihns et al. (U.S. Patent No. 5861366, filed May 1996; cited in the IDS). The teachings of Ihns et al. have been discussed above. Ihns et al. does not teach using the protease cleaning composition for removing protein from glass plates, pipette tips, centrifuge tubes, test tubes, and electrophoresis apparatus.

Claim 14 is directed to the method of claim 13 as described above with the added limitation that the item from which proteins are removed is selected from the group consisting of glass plates, pipette tips, centrifuge tubes, test tubes, and electrophoresis apparatus.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method, as taught by Ihns et al., for protein removal in glass plates, pipette tips, tubes, and electrophoresis apparatus. A person of ordinary skill in the art is motivated to use the method of Ihns et al. for protein removal in glass plates, pipette tips, tubes, and electrophoresis apparatus to eliminate protein contaminants which may interfere with experiments/procedures where these items are used. One of ordinary skill in the art has a reasonable expectation of success at practicing the method of Ihns et al. with items such as glass plates, pipette tips, tubes and electrophoresis apparatus since Ihns et al. uses the protease cleaning composition in food handling equipment. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

20. Claims 15-16 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rojo et al. (Planta 194:328-338, 1994; cited in the IDS). Rojo et al. teaches the isolation, characterization and use of a C. sativus ribonuclease (cusativin) which degrades RNA (page 335, left column, Action on nucleic acids and polynucleotides) and is inactivated at 60 C (page 336, left column, Effects of temperature and

pH on cusativin activity). RNA degradation by cusativin in done in the liquid phase as shown in page 335, Figure 11, caption. Rojo et al. does not teach the use of cusativin to degrade RNA in a liquid sample and the inactivation of cusativin after degradation of RNA in a sample or the use of cusativin to degrade RNA from items.

Claims 15 and 16 are directed in part to a method for enzymatically degrading a nucleic acid or RNA in a sample by using a heat labile nuclease and inactivating the nuclease by heating at no more than 60 C. Claim 20 is directed to the method of claim 15 with the added limitation that the sample is liquid. Claims 18-19 are directed to a method for removing nucleic acids from items such as glass plates, tubes, pipette tips and electrophoresis apparatus.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use cusativin, as taught by Rojo et al., in a method for degrading RNA from a liquid sample or remove RNA from items such as glass plates, tubes, pipette tips or an electrophoresis apparatus, and inactivate cusativin by heating at 60 C after removal/degradation of RNA. A person of ordinary skill in the art is motivated to use cusativin in a method as described above for the benefit of eliminating RNA from samples/items which will be used in protocols/experiments that require RNA-free environments. Also, one of skill in the art is motivated to inactivate cusativin after removal/degradation of RNA to avoid cusativin interfering with subsequent steps in a protocol/experiments. One of ordinary skill in the art has a reasonable expectation of success at using cusativin in a method as described above since Rojo et al. teaches that cusativin will degrade RNA and can be inactivated at 60 C. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

21. Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. (Applied and Environmental Microbiology 64(9):3525-3529, September 1998) in view of Rojo et al.

(Planta 194:328-338, 1994; cited in the IDS). The teachings of Rojo et al. have been discussed above. Rojo et al. does not teach a method of amplifying a DNA molecule in a liquid sample comprising a DNA molecule and a contaminant protein, wherein the sample is treated with an RNase which is inactivated at 60 C. Francis et al. teaches DNA amplification by PCR with DNA from bacterial cells (page 3527, left column, lines 5-26). The PCR samples taught by Francis et al. are in liquid form. The DNA in the PCR samples of Francis et al. contain contaminant proteins since the samples used prior DNA amplification are obtained by lysing bacterial cells without further purification of the samples. Francis et al. does not teach treatment of the samples prior DNA amplification with a nuclease capable of degrading RNA, and inactivation of said nuclease after degradation of RNA.

Claims 21-23 are directed in part to a method of amplifying a DNA molecule in a liquid sample comprising a DNA molecule and a contaminant protein, wherein the sample is treated with an RNase which is inactivated at 60 C. See claim rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the cusativin of Rojo et al. in the method of Francis et al. and further inactivate the cusativin once RNA is degraded. A person of ordinary skill in the art is motivated to use the cusativin in the method of Francis et al. for the benefit of removing RNA impurities which could interfere with PCR. Also, a person of ordinary skill in the art is motivated to inactivate the cusativin prior to amplify the DNA of interest to eliminate additional contaminants. One of ordinary skill in the art has a reasonable expectation of success at using cusativin to degrade RNA in the samples of Francis et al. prior DNA amplification and inactivate cusativin prior to DNA amplification since Rojo et al. teaches that cusativin degrades RNA and that cusativin is inactivated at 60 C. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

22. Claims 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oberto et al. (U.S. Patent No. 4990446, February 1991) in view of Gugi et al. (J. Bacteriol. 173(12):3814-3820, 1991; cited in the IDS). Oberto et al. teaches a method for isolating yeast promoters by digesting DNA and inserting the DNA fragments in a vector which can replicate in yeast and contains the reporter gene lacZ, which encodes β-galactosidase. The DNA fragments are inserted in frame into a site upstream from the lacZ gene (columns 5-6; Figure 1). Oberto et al. does not teach the method for isolating psychrotrophic bacterial promoters. The teachings of Gugi et al. have been discussed above. Gugi et al. also teaches plasmid pMF1 which can be inserted into P. fluorescens. Gugi et al. does not teach a method for isolating psychrotrophic bacterial promoters or a plasmid which contains the β-galactosidase gene.

Claims 24-25 are directed in part to a method for identifying promoters active in psychrotrophic bacteria by operably linking a DNA fragment to a polynucleotide encoding β-galactosidase to create a construct, transforming psychrotrophic bacteria with said construct, and detecting β-galactosidase activity, wherein detection of β-galactosidase activity is indicative of promoter activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice a method, as taught by Oberto et al., for identifying P. fluorescens promoters by inserting the lacZ gene in the pMF1 plasmid, operably linking P. fluorescens DNA fragments downstream from the lacZ gene, transforming P. fluorescens with the modified pMF1 plasmid, and detecting β-galactosidase activity. A person of ordinary skill in the art is motivated to practice the method of Oberto et al. with the P. fluorescens and plasmid of Gugi et al. for the benefit of isolating novel promoters. One of ordinary skill in the art has a reasonable expectation of success at isolating P. fluorescens DNA, modifying the pMF1 plasmid such that it comprises DNA fragments operably linked to the lacZ gene, transforming P. fluorescens with said plasmid, and detecting β-galactosidase since Oberto et al. teaches that method for the identification of yeast promoters, Gugi et al. teaches P. fluorescens and a plasmid which can be inserted in P. fluorescens, and the isolation of DNA from bacteria is well known and widely used in the

art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

23. No claim is in condition for allowance.

24. It is noted that if the references cited are too long, only the relevant pages are being submitted with this Office Action.

25. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 13, 2004

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600